Current Nutrition Reports
https://doi.org/10.1007/s13668-022-00425-0

CANCER (RA MURPHY, SECTION EDITOR)

Intermittent Fasting in Cancer: a Role in Survivorship?

Eleah Stringer[1,2] · **Julian J. Lum**[3,4] · **Nicol Macpherson**[5,6]

Accepted: 18 May 2022

Abstract

Purpose of Review To discuss the historical development of intermittent fasting, its potential underlying mechanisms, and the state of clinical trials, and to reflect on considerations for practice and future recommendations.

Recent Findings Preclinical studies consistently show the robust disease-modifying efficacy of intermittent fasting in various metabolic diseases which may hold implications for cancer prevention and survivorship. Twenty-one clinical trials have or are being conducted on fasting in cancer, utilizing various fasting regimens across different tumor types as a stand-alone intervention or in adjunct to anticancer treatment, with heterogenous outcome variables.

Summary Though there are no known, reproducible diets, to cure or prevent cancer recurrence, preliminary research on the underlying mechanisms, tolerance, and safety of intermittent fasting in cancer warrants further investigation. The inherent flexibility of intermittent fasting to accommodate all types of diets is of necessity in oncology.

Keywords Intermittent fasting · Time-restricted feeding · Oncology · Cancer survivorship

Introduction

Dietary interventions can hold profound health benefits on health promotion and disease prevention. For instance, modifying and monitoring food intake is an important strategy in preventing and managing type II diabetes, hypertension, and other metabolic and chronic diseases. Fasting regimes, including intermittent fasting (IF), are in the spotlight due to the increasing body of evidence demonstrating their potential to ameliorate or, in some cases, reverse disease states. IF is an umbrella term describing diet regimens that cycle between fasting (e.g., abstaining or limiting food and/or drink) and free eating/feeding for a defined period. Preclinical studies in animal models consistently show the robust disease-modifying efficacy of IF on a wide range of chronic disorders, including obesity, diabetes, cardiovascular disease, cancers, and neurodegenerative brain diseases [1••, 2]. This article will review this increasingly popular diet, IF, in the context of cancer survivorship.

With rapidly increasing numbers of cancer survivors [4], there is an increasing patient demand for up-to-date information on nutrition for survivorship. We use the term "cancer survivor" to "describe this broad experience on the cancer continuum — living with, though, and beyond a cancer diagnosis" [5] but acknowledge that everyone affected with cancer may identify with different terms that best express their experience. Research indicates that this group has an ongoing interest in learning cancer information, despite having completed active treatment [6].

A 2021 scoping review including 57 studies on the dietary information needs of adult cancer survivors concluded "dietary information is a needed and valued component of post-treatment survivorship care" and recognizes the importance of survivorship beyond treatment completion. In these studies, cancer survivors frequently report a need for information on dietary strategies to manage cancer and treatment-related side effects as well as on healthy eating behaviors.

This article is part of the Topical Collection on *Cancer*

✉ Eleah Stringer
Eleah.stringer@bccancer.bc.ca

1 Oncology Nutrition, BC Cancer - Victoria, 2410 Lee Ave, Victoria, BC V8R 6V5, Canada

2 Michael Smith Health Research BC, Vancouver, Canada

3 Trev and Joyce Deeley Research Centre, BC Cancer - Victoria, Victoria, Canada

4 Department of Biochemistry and Microbiology, University of Victoria, Victoria, Canada

5 Medical Oncology, BC Cancer - Victoria, Victoria, Canada

6 Faculty of Medicine, University of British Columbia, Vancouver, Canada

Published online: 31 May 2022

There was a preference for specific dietary recommendations and advice that is tailored to individual needs and post-treatment effects and preference for dietitian involvement to assist with lifestyle change as general advice such as "eat well" offered by other health practitioners was not sufficient in meeting their needs [7]. While we have a growing understanding of diet for cancer prevention, less is known about nutrition during survivorship.

Recent progress in understanding metabolic requirements for cancer cell growth calls for a paradigm shift in recognizing cancer as a metabolic disease. Cohort studies and population-level analysis overlook the highly heterogeneous metabolic phenotypes created by an individual's tumor microenvironment and genetic mutations. For example, the metabolic phenotypes of breast cancer cells depend on their molecular subtypes and metastatic sites but can be reprogrammed by intrinsic and extrinsic factors [8]. Nutrition interventions that target metabolism may play a significant role in preventing cancer metastasis and recurrence. Many molecular targeted agents have direct roles on inhibiting specific metabolic processes and pathways that are used to support cancer cell growth and proliferation. Thus, offering dietary interventions may offer a new avenue to curb cancer growth but in a patient-specific manner. This article will discuss the historical development of IF, potential underlying mechanisms, and the state of clinical trials with concluding reflections on considerations for practice and future recommendations.

Intermittent Fasting Then and Now

The fifth-century BCE Greek physician and father of Western medicine, Hippocrates, recommended abstaining from food or drink in patients who exhibited certain symptoms of illness, believing fasting to enable the body to heal itself [9]. Fast forward to the twentieth century and the physiology of fasting in cancer is being uncovered. In 1909, Moreschi observed that tumors transplanted into underfed mice did not grow as well as those transplanted into mice fed ad libitum [10]. Nearly a century later significant research advancements have been made [11••] with key preclinical studies demonstrating the effect of caloric restriction and IF on lifespan [12], the immune response [13], and energy metabolism [14]. In a study by Descamps et al. [15], intermittent fasting significantly reduces the incidence of lymphoma in aged mice as well as in spontaneous tumors while also increasing sensitivity to chemotherapy and radiation therapy [16, 17].

There are multiple variations of IF, cycling between fasting (e.g., abstaining or limiting food and/or drink) and free eating/feeding for a defined period. A lack of standardized terminology and application complicates deciphering and comparing the literature. The term "IF" is commonly used interchangeably with caloric restriction; however, there are important distinctions as caloric restriction requires a reduction in calorie intake by at least 20–40% [18, 19] whereas IF only alters meal timing.

The most common fasting regimens are summarized in Table 1 and include methods such as short-term fasting, caloric restriction, or fasting mimicking diets. When compared to approaches with caloric restriction, IF has gained considerable attention for ease of compliance as there are no restrictions on the types of foods, or caloric intake, and only eating times are altered [20]. This point deserves the spotlight as IF can potentially reach a more diverse population of patients since specific diets such as a low-sodium, diabetic, celiac, vegetarian, and cultural considerations are not barriers.

Cellular Mechanisms That Influence Cancer

During the feeding period, cells engage in tissue-specific processes of growth and plasticity [1••]. Depending on level of physical activity, fasting for 12–24 h typically results in 20% or greater decrease in serum glucose along with hepatic

Table 1 Type and brief description of common fasting regimens

Regimen	Description
Time-restricted feeding	An eating pattern in which no or few calories are consumed for periods that can range from 12 h to several days (usually 12–24 h) on a recurring basis [3]
16/8 method	Is a form of time-restricted feeding (see above) where participants abstain from food/drink for 16 h of the day, eating ad lib for 8 h per day [21]
Short-term fasting	Temporarily fasting (water only), typically for a period between 24 and 48 h [22]
Long-term fasting	With durations between 5 and 21 days can be successfully repeated over a year [21]
Caloric restriction	Reducing calorie intake by 20–40% while maintaining normal meal frequency [18]
Fasting mimicking diet (FMD)	A plant-based, calorie-restricted, low-sugar, low-protein, and high-fat dietary composition administered cyclically and alternated with refeeding periods sufficient to prevent or minimize lean body mass loss [19, 21]
5:2 fasting method	Normal (regular) intake for 5 days of the week, caloric restriction of 600kcals per day for 2 days of the week [21]

glycogen depletion [19]. This necessitates metabolic adaptation to use non-hepatic glucose, fat-derived ketone bodies, and free fatty acids as energy sources. Physiologically, the body acclimates by increasing insulin sensitivity and cellular stress resistance, reducing resting blood pressure and heart rate which is thought to be responsible for many of the health benefits of IF [23, 24]. This insulin feedback can be blocked by dietary modifications which can improve sensitivity to copanlisib, an FDA-approved kinase inhibitor used to treat relapsed follicular lymphoma [25].

Meal timing, circadian rhythm, and metabolism are closely linked. Feeding is a dominant timing cue for the circadian clock in peripheral tissues including the liver (glycogen, cholesterol, and bile acid synthesis versus gluconeogenesis, glycogenolysis, mitochondrial biogenesis), pancreas (insulin versus glucagon secretion), fat (lipogenesis, adiponectin production versus lipid catabolism, leptin secretion), and skeletal muscle (ex. glycolytic versus oxidative metabolism) controlling metabolic pathways [26]. As insulin sensitivity decreases throughout the day and into the night, meals consumed at night are associated with greater post-prandial insulin output contributing to greater risk of developing type 2 diabetes and cardiovascular disease. An inverse relationship has been found between insulin secretion rates and melatonin [27, 28]. Additionally, recent evidence suggests fasting during sleeping hours is associated with a nocturnal rise in plasma free fatty acids, ghrelin, growth hormone, and increased hepatic gluconeogenesis. Adipose tissue controls the uptake, esterification, and release of free fatty acids to meet the metabolic demands of the liver and muscle tissue. Hence, aligning periods of fasting with circadian rhythms may be beneficial [29, 30•, 31••]. Interestingly, during Ramadan which is observed by millions of adult Muslims globally, fasting from dawn to sunset for a lunar month has been shown to improve biochemical and inflammatory profiles including triglycerides, fasting blood sugar, insulin, and HOMA index [32]. This misalignment with the circadian rhythm illustrates the powerful effect of IF.

In animal models, IF has improved cardiometabolic health, reduced cancer incidence, slowed tumor growth, and regenerated organs by increasing stem cell production and lifespan [2, 33]. Human trials demonstrated a reduction in total cholesterol, triglycerides, glucose, insulin, blood pressure, and appetite as well as improvements in insulin sensitivity and lipid profiles [2, 26, 34, 35]. The immune system is also impacted as "IF can affect the development and function of a variety of immune cells, thereby regulating antitumor immune response and affecting tumorigenesis" [11••]. Limiting dietary intake has been shown to shape immunological trajectories, and cause cancer cells to become immunogenic and susceptible to destruction by T cells [36•]. Additionally, IF has been shown to reduce the inflammatory responses such as interleukin 6-mediated and tumor necrosis factor-α-mediated inflammation [2, 26, 34, 36•]. This IF-induced alleviation of inflammation may help to curb the development of many chronic diseases, including obesity, diabetes, vascular diseases, neurodegenerative diseases, and cancer [37, 38].

Based on these metabolic and immunological responses, IF may have dual benefits on inhibiting tumor growth holding implications for cancer prevention and survivorship. A process called differential stress resistance (DSR) helps explain the distinct molecular riposte of healthy versus tumor cells. During nutrient deprivation, healthy cells reinvest energy in maintenance and repair, while tumor cells are unable to slow down growth due to mutations in tumor suppressor genes (e.g. Pas, Akt, mTOR, Rb, TP53, PTEN) and mitogenic pathways [39–41]. This strengthens healthy cells while rendering cancer cells susceptible to chemotherapy [42]. Furthermore, low serum levels of glucose during fasting impose extra stress on tumor cells, as their energy needs under these circumstances are primarily met by glucose metabolism. As a consequence of these differential responses of healthy versus cancer cells to fasting, tumor cells are unable to enter a protective state and have impaired energy metabolism [42]. Impaired glycolysis limits outgrowth due to absence of nutrients [43]. This suggests by limiting nutrient availability through IF in patients with minimal residual disease post-therapy can stop the resurgence of quiescent cancer cells.

Aside from DSR, autophagy is notable cellular process that may be exploited for oncological benefits. In 2016, Dr. Yoshinori was awarded a Nobel Prize in Physiology and Medicine for groundbreaking discoveries in the identification of the genetic pathway controlling autophagy, the process by which organisms remove damaged or dying cells. Subsequently, a large body of literature has uncovered many benefits of autophagy that are associated with longevity, healthy aging, and mitigating cancer development [44–46]. Autophagy is activated during periods of nutrient limitation including caloric restriction, IF, or when damage has occurred within the cell [47••, 48]. Several studies have shown that limiting glucose or other nutrients in model organisms such as nematode worms and fruit flies activates survival by autophagy. A prevailing idea is that reducing nutrient uptake and metabolic activity places cells in a state of "stasis" which serves dual functions [49]. First, it allows cells the opportunity to engage in repair, and second, it reduces the chance of producing toxic free radicals [44]. Jamshed et al. [30•] conducted the first clinical study to determine how time-restricted feeding affects gene expression, amongst other measures, and found increased expression of the autophagy gene *LC3A* by 22% in the mornings at the end of the 18-h fast.

Despite the rapid growth in these mechanisms, the heterogeneity of fasting applications and limited clinical trials hinders the ability to tease apart the underlying mechanisms and draw reliable conclusions [50]. Recent advancements in tissues, biofluid, and cell-based metabolomics, however, offer a new sensitive tool to detect changes in metabolic process that may help identify pathways that are most impacted by IF in a cell-specific manner.

State of Clinical Trials

A 2020 systematic review examined the effect of IF on cancer prevention assessing 307 reports including six preclinical studies. Most studies concluded that IF had a positive effect on reducing the risk of cancer incidence or development by reducing tissue inflammation and number of lesions. The authors conclude that animal experiments indicate a possible preventative effect of IF on certain types of cancers and that "future well-designed randomized clinical trials should examine the effect of intermittent fasting over longer periods of time, parallel forms of cancer and different patient populations" [50].

Most available studies on fasting in cancer are preclinical, conducted in vitro or in animals, with a scant amount of literature in human interventional trials in oncology. It is evident, however, that clinical trials are becoming more prevalent, warranting a systematic review of the evidence in the near future. To describe the landscape of current studies, a search of clinicaltrials.gov was conducted on February 22, 2022, using combinations of the following search terms: "fasting," "intermittent fasting," "time restricted feeding," "cancer," and "oncology." This revealed 21 interventional trials of fasting in cancer. Depicted in Fig. 1, the first trial was conducted in 2009 and shows the increasing interest in the potential benefits of IF in patients with cancer. At the present time, there are 12 active clinical trials on fasting in chronic lymphocytic leukemia/small lymphocytic lymphoma, breast cancer, and prostate cancer.

Seventy percent of these studies test the application of short-term fasting around chemotherapy and/or immunotherapy administration. In 2019, de Groot et al. found short-term fasting reduced treatment toxicity and was safe and feasible in patients with cancer. The application of this regimen is finding consistent results and remains a promising area of interest in fasting for cancer. The newest trial started in 2020 testing short-term fasting for 37 to 48 h prior to immunotherapy administration and for 24 h following infusion in patients with advanced or metastatic skin malignancy (NCT04387084). The primary objectives are to evaluate the safety, feasibility, adherence, and fasting-related toxicity [51]. Though short-term fasting continues to be an area of interest, as indicated by the triangles in Fig. 1, the overarching trend is tending towards investigating time-restricted feeding (TRF) with 75% of the trials on TRF having started in the past 18 months. TRF is an eating pattern in which no or few calories are consumed for periods that can range from 12 h to several days (usually 12–24 h) on a recurring basis (see Table 1).

The first clinical trial to test the effect of TRF, defined as a minimum of 14-h fasting per day during Ramadan, was conducted by Badar et al. in 2014 for the purpose of assessing the feasibility and safety of fasting while receiving chemotherapy and to "compare the impact of fasting versus non-fasting on the side effect profile of the chemotherapeutic regimen received" [52]. It was

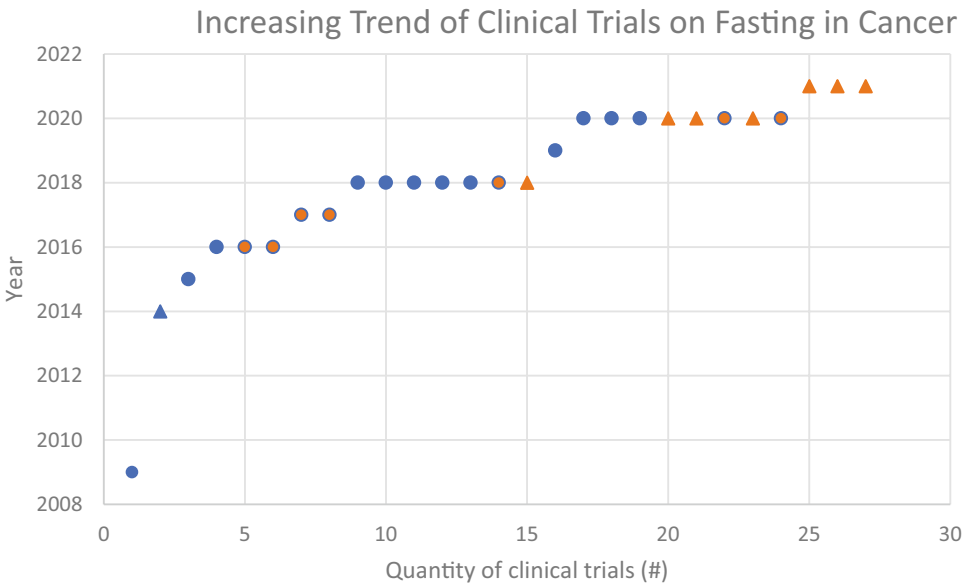

Fig. 1 Increasing trend of clinical trials on fasting in cancer. Triangles indicate trials on time-restricted feeding (TRF); circles indicate fasting regimes other than TRF; blue markers indicate a completed status; orange markers indicated an active status. Data compiled from search of clinicaltrials.gov on Feb 22, 2022

conducted in a heterogenous group of 11 patients with lymphoma, leukemia, and cancers of the nasopharynx, breast, colon, and ovaries, and found a significant decrease in chemotherapy-induced side effects, most notably fatigue, weakness, vomiting, and diarrhea compared to chemotherapy alone and did not interfere with chemotherapy efficacy. Furthermore, they "did not find alarming spikes/ changes in blood biomarkers or deterioration of symptoms" or weight during fasting compared to ad lib intake. The six current active clinical trials on TRF are summarized in Table 2.

Of these active trials, diet adherence, completion rates, and participant safety are the dominating primary endpoints. Our study at BC Cancer (NCT04626843) is also measuring patient-reported changes in quality of life, an outcome of particular interest in survivorship, through serial administration of the EORTC Core Quality of Life Questionnaire (QLQ-C30) [53]. Though clinical cancer markers such as PSA doubling time and breast tumor cell proliferation are measured in some studies, the two studies in cancer survivors who have completed anticancer treatment (NCT03523377 and NCT04691999) have not indicated measures of cancer outcomes.

The first trial in survivorship (NCT03523377) is in childhood cancer survivors. All participants are adults, over the age of 18, who are at least 2 years out of treatment. The aim of this study is "to test whether regularly not eating for at least 14 h overnight ('intermittent fasting') is feasible and can improve blood sugar" [54]. At the time of writing, the trial is still recruiting with an estimated study completion date of April 2024. To our knowledge, this is the first study on intermittent fasting in cancer survivors.

The second trial (NCT04691999) is in a group of breast cancer survivors who have completed chemotherapy (adjuvant endocrine therapy is permitted) prior to initiation of the trial. Their primary outcome measures are adherence to the fasting program and changes in body fat. The aim of their study is "to incorporate this dietary strategy as a standard component of care for breast cancer patients" [55].

Though these studies are on the way to expanding the metabolic impacts of intermittent fasting, there are undeniable challenges to assessing their effects on cancer control. Two approaches can be taken: large trials for statistical validation or smaller randomized control trials with deep analysis. Once studies involve chemotherapy and/or immunotherapy, the systemic therapy intervention further confounds results. Assessing the impact of nutrition interventions in cancer survivorship on delaying recurrence or improving survival holds the additional challenge due to the long follow-up period required in the study design.

Table 2 Active clinical trials on time-restricted feeding (TRF) in cancer

Trial, site	*N*	Registration date	Tumor, treatment type*	IF regime	Primary endpoint
NCT03523377, Memorial Sloan Kettering Cancer Center	40	May 2018	Any, history of treatment but off treatment for 2 + yrs	Min. 14-h fasting overnight × 6 mo	Completion rates, glucose metabolism
NCT04691999, Duke University	36	Dec 2020	Breast cancer, completed CX	16–18-h fasting 4 days/wk × 6 mo	Adherence, body composition
NCT04288336, Mayo Clinic	25	Feb 2020	Localized high-risk prostate cancer, post-RP	16-h fast daily × 1 yr	Adherence, PSA kinetics/doubling time
NCT04708860, Dana-Farber Cancer Institute	30	Jan 2021	Met breast, initiating EN	Min. 13-h fast, no eating after 8 pm, min. 6d/wk × 12wk	Feasibility, adherence to diet and exercise
NCT04626843, BC Cancer	20	Nov 2020	CLL/SLL; active surveillance only	16-h fast, min. 6 days/wk × 3 mo	Changes in lymphocyte count, quality of life, inflammation, metabolic profiles, autophagy status, immune cell gene expression profiles, gut microbiome
NCT05023967, MD Anderson Cancer Centre, Galliera Hospital	120	Aug 2021	Breast, pre-SX	Min 16-h fast × 4–6 wks, in combo with metformin hydrochloride ER	Safety, tumor cell proliferation, biomarkers of Br cancer
NCT05083416, Moffatt Cancer Centre	52	Sept 2021	Advanced head and neck SCC, IT	8–10-h feeding window × 3 mo	Adherence, change in gut microbiome and microbial metabolites

**RT*, radiation therapy; *SX*, surgery; *CX*, chemotherapy; *RP*, radical prostatectomy; *EN*, endocrine therapy in combo with palbociclib or alpelisib; *IT*, immunotherapy

Considerations for Practice and Future Recommendations

The nutrition needs of cancer survivors are unique and individualized based on cancer and treatment history, side effects, performance status, and nutritional risk factors and should consider survivors' personal health goals and values. Even upon completing anticancer therapy, survivors remain at risk for malnutrition secondary to medical and surgical treatments. Maintaining adequate intake that accounts for resting energy expenditure, activity level, and diet-induced thermogenesis is imperative for preserving a stable, nutritional state [56].

It is recommended to take nutrition guidance from an oncology dietitian who can provide a comprehensive nutrition assessment and collaborate with the healthcare team to determine appropriate diet recommendations that are patient-centered and align with medical treatment goals. While "there are no diets known to reproducibly cure cancer or prevent cancer recurrence" [56], several features of IF regimes, specifically TRF, make this an intriguing diet warranting future studies in cancer survivorship:

1. Calories and protein are not restricted: Within the eating window, any quantity of food and fluid can be consumed. For example, high-protein and high-calorie diet choices can be followed if deemed medically and/or nutritionally required.
2. It can accommodate dietary preferences and restrictions: Any food and fluid can be consumed (or avoided) during the eating window. While most diets prescribe specific combinations of food and fluids, TRF alters eating times only. This is significant as it can accommodate other diets commonly prescribed through medical nutrition therapy during cancer treatment and recovery such as a fiber-restricted diet, tyramine-restricted diet, or texture-modified diet. Additionally, it entertains patient food preferences.
3. There is inherent flexibility: The eating window in TRF can be chosen to best align with one's daily routine. For example, early risers may prefer their eating window earlier in the day, while others may opt to begin eating at noon. Three of the four active clinical trials allow for at least one "cheat day" per week (NCT04691999, NCT04708860, NCT04626843).
4. People may feel better: Generally, diets are easiest to follow when they increase a sense of wellness. Research in healthy individuals demonstrates people see an improvement in their energy, sleep, and overall mood on IF [26, 34] contributing to its acceptability.

Before clinical recommendations can be made on IF during cancer treatment or survivorship, there is a strong need for:

1. Rigorous methodology: Quality study design is needed to reduce biases and control for variables
2. Better comparability between studies: Detailed descriptions of IF and outcomes measures are needed to overcome barriers in comparing results.
3. Understanding the patient experience: Patient feedback and experience with IF should be qualitatively described, to provide insight into the practicality of diet manipulation and impact on quality of life.
4. Rates of adherence: Tightly linked to the patient experiences, rates of adherence should be reported throughout the trajectory of the study to provide insight into potential barriers and facilitators, in both the short and long terms.

Conclusion

IF, particularly TRF, is an intriguing diet regimen for research consideration due to its potential molecular mechanisms targeting the immune system and dysregulation of cancer metabolism. Fasting, however, may be contraindicated in some cancer survivors. It is recommended to seek medical and dietetics expertise during cancer survivorship. While IF appear promising as a dietary intervention that does not alter composition, trials are in their infancy, so it is too early to draw conclusions on the benefit of IF during cancer treatment or in survivorship. Further research is needed on IF in cancer survivorship to help elucidate the differences between various fasting regimens on acceptability and effectiveness [57]. Special attention should be paid to clinical outcomes, changes in body weight and composition, acceptability, and impact on quality of life. Lastly, there is a pervading necessity to elucidate clear, concise, and evidence-based nutrition guidelines for cancer survivorship to help meet the unique diet information needs of this group.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13668-022-00425-0.

Compliance with Ethical Standards

Conflict of Interest Eleah Stringer is funded by Michael Smith Health Research BC and the Lotte & John Hecht Memorial Foundation. Julian Lum has received a research grant from the Canadian Institute for Health Research and is the Director of The Metabolomics Consortium of BC (MetaboBC). Nicol Macpherson declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.•• de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. N Engl J Med. 2019;381(26):2541–51. **This review provides an excellent overview of the cellular and molecular mechanisms underlying intermittent metabolic switching and is authored by two global leaders on intermittent fasting in cancer.**
2. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev. 2017;39:46–58.
3. Anton SD, Moehl K, Donahoo WT, Marosi K, Lee SA, Mainous AG, et al. Flipping the Metabolic switch: understanding and applying the health benefits of fasting. Obesity. 2018;26(2):254–68.
4. Halpern MT, McCabe MS, Burg MA. The cancer survivorship journey: models of care, disparities, barriers, and future directions. Am Soc Clin Oncol Educ Book. 2016;36:231–9.
5. The NCCS Definition of a "Cancer Survivor" [Internet]. NCCS - National Coalition for Cancer Survivorship. 2014 [cited 2022 Jan 26]. Available from: https://canceradvocacy.org/defining-cancer-survivorship/.
6. Shea-Budgell MA, Kostaras X, Myhill KP, Hagen NA. Information needs and sources of information for patients during cancer follow-up. Curr Oncol Tor Ont. 2014;21(4):165–73.
7. Johnston EA, van der Pols JC, Ekberg S. Needs, preferences, and experiences of adult cancer survivors in accessing dietary information post-treatment: a scoping review. Eur J Cancer Care (Engl). 2021;30(2): e13381.
8. Wang L, Zhang S, Wang X. The metabolic mechanisms of breast cancer metastasis. Front Oncol [Internet]. 2021 [cited 2022 Mar 19];10. Available from: https://www.frontiersin.org/article/10.3389/fonc.2020.602416.
9. fasting | Definition, Description, Types, Benefits, & Facts [Internet]. Encyclopedia Britannica. [cited 2021 Jul 16]. Available from: https://www.britannica.com/topic/fasting.
10. Kritchevsky D. Caloric restriction and cancer. J Nutr Sci Vitaminol (Tokyo). 2001;47(1):13–9.
11.•• Zhao X, Yang J, Huang R, Guo M, Zhou Y, Xu L. The role and its mechanism of intermittent fasting in tumors: friend or foe? Cancer Biol Med. 2021;18(1):63–73. **This review article discussed the role of intermittent fasting in tumorigenesis and tumor therapy.**
12. Weindruch R, Sohal RS. Caloric intake and aging. N Engl J Med. 1997;337(14):986–94.
13. Prokopenko LG, Nikolaeva IA, Baĭburin FI, Kotel'nikova LV. The immunomodulating action of intermittent fasting under temperature, toxic and food loads. Patol Fiziol Eksp Ter. 1998;(4):15–7.
14. Harvie M, Howell A. Energy restriction and the prevention of breast cancer. Proc Nutr Soc. 2012;71(2):263–75.
15. Descamps O, Riondel J, Ducros V, Roussel A-M. Mitochondrial production of reactive oxygen species and incidence of age-associated lymphoma in OF1 mice: effect of alternate-day fasting. Mech Ageing Dev. 2005;126(11):1185–91.
16. O'Flanagan CH, Smith LA, McDonell SB, Hursting SD. When less may be more: calorie restriction and response to cancer therapy. BMC Med. 2017;15(1):106–106.
17. Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. Nat Rev Cancer. 2018;18(11):707–19.
18. Antunes F, Erustes AG, Costa AJ, Nascimento AC, Bincoletto C, Ureshino RP, et al. Autophagy and intermittent fasting: the connection for cancer therapy? Clinics [Internet]. 2018 [cited 2019 Sep 23];73. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6257056/.
19. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab. 2014;19(2):181–92.
20. Barnosky AR, Hoddy KK, Unterman TG, Varady KA. Intermittent fasting vs daily calorie restriction for type 2 diabetes prevention: a review of human findings. Transl Res J Lab Clin Med. 2014;164(4):302–11.
21. de Toledo FW, Grundler F, Sirtori CR, Ruscica M. Unravelling the health effects of fasting: a long road from obesity treatment to healthy life span increase and improved cognition. Ann Med. 2020;52(5):147–61.
22. Turbitt WJ, Demark-Wahnefried W, Peterson CM, Norian LA. Targeting glucose metabolism to enhance immunotherapy: emerging evidence on intermittent fasting and calorie restriction mimetics. Front Immunol [Internet]. 2019 Jun 25 [cited 2021 May 6];10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6603129/.
23. Fontana L, Partridge L, Longo VD. Extending healthy life span—from yeast to humans. Science. 2010;328(5976):321–6.
24. Mager DE, Wan R, Brown M, Cheng A, Wareski P, Abernethy DR, et al. Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. FASEB J Off Publ Fed Am Soc Exp Biol. 2006;20(6):631–7.
25. Hopkins BD, Pauli C, Du X, Wang DG, Li X, Wu D, et al. Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature. 2018;560(7719):499–503.
26. Patterson RE, Sears DD. Metabolic effects of intermittent fasting. Annu Rev Nutr. 2017;37(1):371–93.
27. Boden G, Ruiz J, Urbain JL, Chen X. Evidence for a circadian rhythm of insulin secretion. Am J Physiol. 1996;271(2 Pt 1):E246-252.
28. Stenvers DJ, Scheer FAJL, Schrauwen P, la Fleur SE, Kalsbeek A. Circadian clocks and insulin resistance. Nat Rev Endocrinol. 2019;15(2):75–89.
29. Stockman M-C, Thomas D, Burke J, Apovian CM. Intermittent fasting: is the wait worth the weight? Curr Obes Rep. 2018;7(2):172–85.
30.• Jamshed H, Beyl RA, Della Manna DL, Yang ES, Ravussin E, Peterson CM. Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, Aging, and autophagy in humans. Nutrients. 2019;11(6):1234. **This randomized cross-over study measured the effect of time-restricted feeding on autophagy and circadian clock gene expression.**
31.•• Mindikoglu AL, Abdulsada MM, Jain A, Choi JM, Jalal PK, Devaraj S, et al. Intermittent fasting from dawn to sunset for 30 consecutive days is associated with anticancer proteomic signature and upregulates key regulatory proteins of glucose and lipid metabolism, circadian clock, DNA repair, cytoskeleton remodeling, immune system and cognitive function in healthy subjects. J Proteomics. 2020;15(217): 103645. **The results of this trial hold important clinical implications, suggesting that intermittent fasting from dawn to sunset can be a preventative and adjunct therapy in cancer.**
32. Mohammadzade F, Vakili MA, Seyediniaki A, Amirkhanloo S, Farajolahi M, Akbari H, Eshghinia S, et al. Effect of prolonged intermittent fasting in Ramadan on Biochemical and inflammatory parameters of healthy men. J Clin Basic Res. 2017 May 1;1(1):38–46.
33. Tinsley GM, Horne BD. Intermittent fasting and cardiovascular disease: current evidence and unresolved questions. Future Cardiol. 2018;14(1):47–54.

34. Rothschild J, Hoddy KK, Jambazian P, Varady KA. Time-restricted feeding and risk of metabolic disease: a review of human and animal studies. Nutr Rev. 2014;72(5):308–18.
35. Nowosad K, Sujka M. Effect of Various types of intermittent fasting (IF) on weight loss and Improvement of diabetic parameters in human. Curr Nutr Rep. 2021;10(2):146–54.
36.• Collins N, Belkaid Y. Control of immunity via nutritional interventions. Immunity. 2022;55(2):210–23. **This review discusses how nutrition in industrialized countries has fundamentally altered the way our immune system is wired.**
37. Di Francesco A, Di Germanio C, Bernier M, de Cabo R. A time to fast. Science. 2018;362(6416):770–5.
38. Rajpal A, Ismail-Beigi F. Intermittent fasting and "metabolic switch": effects on metabolic syndrome, prediabetes and type 2 diabetes. Diabetes Obes Metab. 2020;22(9):1496–510.
39. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57–70.
40. Raffaghello L, Lee C, Safdie FM, Wei M, Madia F, Bianchi G, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proc Natl Acad Sci U S A. 2008;105(24):8215–20.
41. Schumacher B, Garinis GA, Hoeijmakers JHJ. Age to survive: DNA damage and aging. Trends Genet. 2008;24(2):77–85.
42. de Groot S, Pijl H, van der Hoeven JJM, Kroep JR. Effects of short-term fasting on cancer treatment. J Exp Clin Cancer Res. 2019;38(1):1–14.
43. Bailey C, Black JRM, Reading JL, Litchfield K, Turajlic S, McGranahan N, et al. Tracking Cancer evolution through the disease course. Cancer Discov. 2021;11(4):916–32.
44. Mizushima N, Levine B. Autophagy in human diseases. N Engl J Med. 2020;383(16):1564–76.
45. Martinez-Lopez N, Tarabra E, Toledo M, Garcia-Macia M, Sahu S, Coletto L, et al. System-wide benefits of intermeal fasting by autophagy. Cell Metab. 2017;26(6):856-871.e5.
46. Mani K, Javaheri A, Diwan A. Lysosomes mediate benefits of intermittent fasting in cardiometabolic disease: the janitor is the undercover boss. Compr Physiol. 2018;8(4):1639–67.
47.•• Cozzo AJ, Coleman MF, Pearce JB, Pfeil AJ, Etigunta SK, Hursting SD. Dietary energy modulation and autophagy: exploiting metabolic vulnerabilities to starve cancer. Front Cell Dev Biol. 2020;8:590192. **This review discusses reprogramming cancer cell metabolism with a focus on autophagy induction, inhibition, or both as therapeutic strategies to improving cancer outcomes.**
48. Lum JJ, Bauer DE, Kong M, Harris MH, Li C, Lindsten T, et al. Growth factor regulation of autophagy and cell survival in the absence of apoptosis. Cell. 2005;120(2):237–48.
49. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. Nat Rev Mol Cell Biol. 2020;21(4):183–203.
50. Giannakou K, Papakonstantinou C, Chrysostomou S, Lamnisos D. The effect of intermittent fasting on cancer prevention: a systematic review. Eur J Public Health [Internet]. 2020 Sep 1 [cited 2021 Apr 28];30(ckaa166.216). Available from: https://doi.org/10.1093/eurpub/ckaa166.216.
51. University of Southern California. Short-term fasting prior to standard checkpoint blockade using PD-1/PD-L1 inhibition: a pilot safety and feasibility study [Internet]. clinicaltrials.gov; 2021 Apr [cited 2022 Mar 14]. Report No.: NCT04387084. Available from: https://clinicaltrials.gov/ct2/show/NCT04387084.
52. Badar T. Safety and feasibility of Muslim fasting while receiving chemotherapy. In 2014.
53. EORTC Quality of Life website | EORTC Quality of Life Group website [Internet]. EORTC – Quality of Life. [cited 2019 Oct 14]. Available from: https://qol.eortc.org/.
54. Memorial Sloan Kettering Cancer Center. Overnight fasting after completion of therapy: the OnFACT study [Internet]. clinicaltrials.gov; 2021 Dec [cited 2022 Feb 21]. Report No.: NCT03523377. Available from: https://clinicaltrials.gov/ct2/show/NCT03523377.
55. Duke University. EFFECT-BC: the effect of intermittent Fasting on body composition in women with breast cancer [Internet]. clinicaltrials.gov; 2021 Nov [cited 2022 Mar 17]. Report No.: NCT04691999. Available from: https://clinicaltrials.gov/ct2/show/NCT04691999.
56. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, et al. ESPEN practical guideline: clinical nutrition in cancer. Clin Nutr. 2021;40(5):2898–913.
57. Chung HY, Kim DH, Bang E, Yu BP. Impacts of calorie restriction and intermittent fasting on health and diseases: current trends. Nutrients. 2020;12(10):2948.